Botulinum toxin treatment of spasmodic torticollis

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Summary

We reviewed the efficacy and adverse effects of repeated botulinum toxin injections into hyperactive neck muscles of 107 successive patients with spasmodic torticollis. They received 510 injection treatments over a median period of 15 months (range 3-42 months). One patient failed to benefit at all, but 101 (95%) patients reported considerable (moderate or excellent) benefit from at least one treatment. On a global subjective response rating, 93% of 429 treatments resulted in some improvement and 76% in moderate or excellent improvement. Pain reduction followed 89% of 190 treatments with moderate or excellent reduction after 66%. Median duration of benefit was 9 weeks. All torticollis types responded equally well and injections into two (or more) involved neck muscles were more effective than injection into a single muscle. The most frequent adverse effect was dysphagia, occurring after 44% of all treatments, but this was severe after only 2%. Antibodies to botulinum toxin were detected in the serum of three out of the five patients in whom loss of treatment efficacy occurred. We conclude that botulinum toxin treatment is the most effective available therapy for spasmodic torticollis and practical advice is provided for anyone wishing to set up the technique.

Introduction

Spasmodic torticollis, which usually presents in adult life, is the most common focal dystonia[1]. Patients are distressed by neck pain, functional disability and social embarrassment. Until recently torticollis has been notoriously difficult to treat. A variety of drugs, principally anticholinergics, and surgery were the main therapeutic options. Both often failed to control the torticollis, and unwanted side effects were common with drugs[2]. The advent of treatment with injections of botulinum toxin, type A, (BOTOX), a potent neurotoxin producing temporary muscle weakness by presynaptic inhibition of acetylcholine release[3], has considerably altered the management of spasmodic torticollis.

A number of small blinded, placebo-controlled trials of BOTOX treatment of torticollis have shown significant benefit[4-6], as have several uncontrolled studies[7-11]. This success, confirmed by the results in the present paper, means that it will be desirable to provide BOTOX treatment at a number of centres throughout the UK and elsewhere so as to make this therapy widely available. The purpose of this paper is to describe the practical methods, results and complications of this new treatment, based upon a series of 107 patients so managed in the last three and half years. We will concentrate upon those issues of importance to anyone wishing to set up the technique.

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Patients and methods

Patients

The 107 patients attended The National Hospital for Neurology and Neurosurgery for treatment of torticollis by botulinum toxin injection. This does not represent the total number of such cases seen at this hospital, for others were treated by colleagues, and in some cases there was insufficient information for analysis. There were 65 females and 42 males, with a median age of 47 years (range 22-80 years). Median age of onset of torticollis was 40 years (range 3-77 years), with a median duration of symptoms of 5 years (range 1-42 years). Twenty-eight patients (26%) had dystonia elsewhere (six generalized dystonia, 22 cranio-cervical dystonia), and 28 (26%) had bilateral hand tremor. Sixteen patients (15%) developed their torticollis within a year of local neck trauma. Ninety-eight (92%) had been given drug therapy without significant benefit, and seven (6.5%) had had prior surgical treatment. Fifty-seven (53%) had predominant rotatory torticollis (34 left and 23 right), 15 (14%) laterocollis (11 left and 4 right), 15 (14%) complex or chaotic torticollis with no single head and neck posture predominating, 11 (10%) retrocollis, and nine (8%) dystonic head tremor.

Assessment

The appropriate muscles for injection were identified on clinical examination in the following standard manner. Patients were first asked to identify any site of neck pain or discomfort. In our experience this is usually the location of a hyperactive muscle. The patients were then instructed to let the head to 'do what it wants to', so as to allow the head and neck to adopt their usual position without 'fighting against it', and not to employ any geste antagoniste. Head position, visible muscle hyperactivity and head tremor were noted. The neck was then palpated to detect muscle tenderness and/or hyperactivity. Finally the patient was observed whilst walking for any additional posturing of the head and neck and associated muscle hyperactivity.

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Table 1. Recommendations for botulinum toxin treatment of torticollis

Type of torticollis	*Muscles to be injected*†	*BOTOX dose (MU‡)* *Normal neck*	*Thin neck*
Rotatory	Contralateral sternomastoid	300	200
	Ipsilateral splenius capitis	500	400
Retrocollis	Left splenius capitis	500	400
	Right splenius capitis	500	400
	Trapezius or semispinalis capitis if splenii injections ineffective		
Laterocollis	Ipsilateral sternomastoid	300	200
	Ipsilateral splenius capitis	400	300
	Ipsilateral trapezius	400	300
Dystonic head tremor	Left splenius capitis	500	400
	Right splenius capitis	500	400
Complex torticollis	Left splenius capitis	500	400
	Right splenius capitis	500	400
	One active sternomastoid	300	200
Shoulder elevation	Ipsilateral trapezius	400	400
First principles	(i) Inject painful or tender muscles		
	(ii) Inject visibly or palpably hyperactive muscles		
	(iii) Inject muscles according to the type of torticollis		

* Single injections to each muscle
* Avoid injecting both sternomastoid muscles at the same visit, or within 6 weeks of each other as severe dysphagia may result
* Inject the sternomastoid muscle as rostral as possible (close to its insertion into the mastoid process), to minimize risk of dysphagia
* Patients with existing neuromuscular disorders should be treated with caution or not at all

†Direction of torticollis is indicated by the direction of chin rotation; muscles to be injected designated with respect to direction of chin rotation
‡MU indicates mouse units of botulinum toxin (Porton Down UK) injected

Injection

The muscles for injection were selected according to the strategy outlined in Table 1. Injections were delivered to (i) painful or tender muscles; (ii) visibly or palpably hyperactive muscles. If neither of the above criteria could be applied, or if additional muscles were thought to be involved, further muscles to be injected were selected on the basis of the type of torticollis as classified in Table 1. The botulinum A toxin was supplied by the Centre for Applied Microbiology and Research, Porton Down, Wiltshire, UK (see appendix). Each ampoule contained 50 ng (2000 mouse units [MU], one MU being the LD50 for mice) of freeze dried toxin bound to haemagglutinin. Each ampoule was reconstituted immediately before injection with 10 ml isotonic saline. The resulting

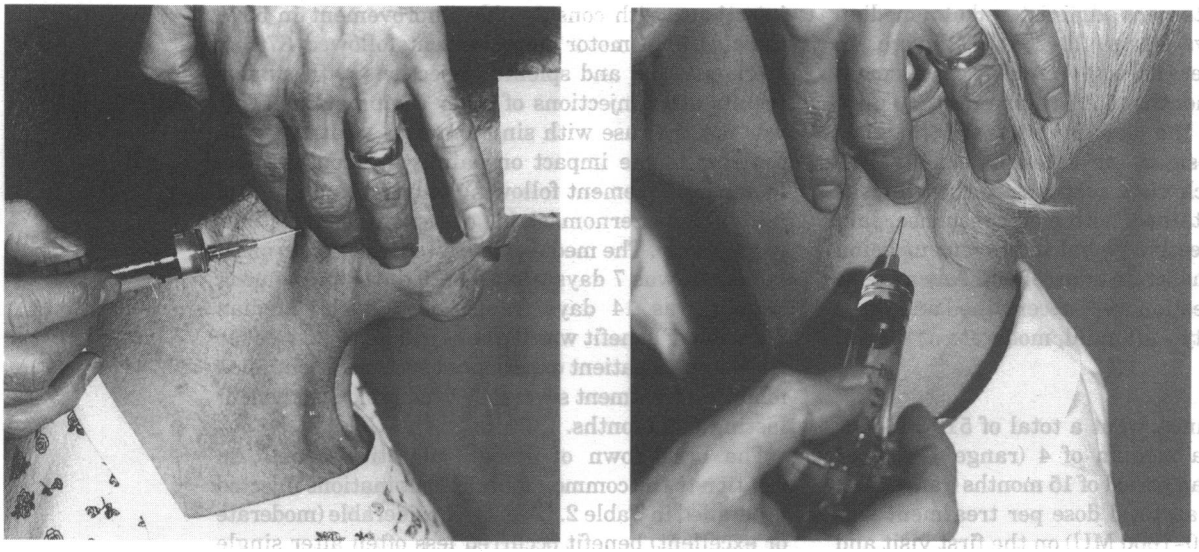

Figure 1. Sites and technique of botulinum toxin injection into the neck muscles of torticollis patients. (left) Sternomastoid injection: The muscle is grasped between two fingers and the injection is delivered as rostral (ie, close to its insertion into the mastoid process) as is possible, into the posterolateral fibres. (right) Splenius Capitis injection: First the sternomastoid is defined between the index and middle fingers. The splenius, which is located just posterior and deep to the sternomastoid, can then be palpated/rolled beneath the tip of the most posterior of these two fingers (in this illustration the middle finger). The injection is delivered into this location taking care to avoid injection into the venous plexus which lies deep to the splenius. Trapezius injection (not depicted): the trapezius muscle is grasped between the thumb and index fingers at the base of the neck where it is relatively superficial. The injection is delivered into the muscle between the two fingers

Table 2. Global subjective response to 429 botulinum toxin treatments

Injected muscles	Number of treatments	Improvement: Nil n†	Nil (%)‡	Mild n	Mild (%)	Moderate n	Moderate (%)	Excellent n	Excellent (%)
Sternomastoid and splenius	189	11	(5.8)	27	(14.3)	99	(52.4)	52	(27.5)
Both splenii	66	2	(3.0)	6	(9.0)	32	(48.5)	26	(39.4)
One splenius	33	6	(18.2)	10	(30.3)	12	(36.4)	5	(15.2)
One sternomastoid	19	3	(15.8)	5	(26.3)	7	(36.8)	4	(21.2)
Trapezius and splenius	36	1	(2.8)	7	(19.4)	21	(58.3)	7	(19.4)
Trapezius, splenius and sternomastoid	38	2	(5.3)	13	(34.2)	13	(34.2)	10	(26.3)
Other combinations	48	4	(8.3)	7	(14.6)	29	(60.4)	8	(16.7)
Total	429	29	(6.8)	75	(17.5)	213	(49.7)	112	(26.1)

†n=number of treatments; ‡n=percentage of treatments

solution (5 ng or 200 MU per ml) was drawn up into a 10 ml syringe. The injections were delivered via a 1 inch, 25 needle. The dose to each muscle was administered into a single site (Figure 1), as our experience had previously been that multiple injections into a single muscle conferred no better results than single injections[12]. Sternomastoid injections were delivered into the most rostral site possible as we have found that this strategy reduces the incidence of dysphagia.

It is important for practitioners to be aware of the difference in relative potencies of the UK and North American BOTOX preparations, the latter (Oculinum) distributed by Allergan Pharmaceuticals. Whereas 1 ng of the North American toxin is equivalent to 2.5 MU, 1 ng of the UK preparation from Porton Down is equivalent to 40 MU. This difference in potency of the two toxins may in part explain the different doses employed on either side of the Atlantic.

Early in this series we injected a standard dose of 500 MU into each muscle. However, because patients developed side effects, subsequent doses usually were decreased, and we now use the doses shown in Table 1.

Repeat treatments were administered at a median interval of 84 days (range 10-289). Although, in general, patients were asked to return for assessment and reinjection 3 months after treatment, they were treated earlier if the benefit from the previous injection had subsided, or later if benefit was maintained. At each visit, response to the previous injection was ascertained, with motor response, pain reduction and subjective global improvement being rated as nil, mild, moderate or excellent. Any adverse effects from the injection were ascertained and rated on a scale of severity - nil, mild, moderate or severe.

Results

The 107 patients underwent a total of 510 BOTOX treatments, with a median of 4 (range 1-13) per patient over a median period of 15 months (range 3-42 months). The median total dose per treatment was 1000 MU (range 200-1600 MU) on the first visit and 800 MU (range 140-1400 MU) on subsequent visits.

Only one patient failed to benefit at all from repeated injections, whilst 101 of the other 106 patients (95%) obtained considerable benefit (moderate or marked improvement) from at least one of their treatments. For this reason, and because the variation in response to individual injections meant that treatments were tailored to the neck posture/muscle hyperactivity pattern present at each visit, we have elected to analyse the response/benefit by individual treatments rather than by patients.

In 429 of the 510 treatments reviewed it was possible to determine the nature of the patients subjective response. There was no improvement after 29 injections, but 400 (93%) of the treatments resulted in some benefit; in 325 (76%) there was considerable (moderate or excellent) improvement. The most common muscle combination injected was ipsilateral splenius and contralateral sternomastoid, comprising 44% of the 429 treatments. There was considerable improvement after 80% of such injections (Table 2). Pain response was specified following 190 of the treatments. There was some improvement in pain after 89%, with considerable (moderate or excellent) reduction after 66% of treatments. There was considerable pain reduction in the same proportion (66%) of sternomastoid and splenius injections, with similar results for all muscle combinations including those into single muscles. Details of motor response (spasms, head position) were specified following 214 treatments.

There was motor improvement following 89% of injections, with considerable improvement in 59%. Considerable motor improvement followed 67% of sternomastoid and splenius injections with similar results after injections of other combinations. This was not the case with single muscle treatments (in contrast to the impact on pain), with considerable motor improvement following only 11% and 39% of individual sternomastoid or splenius injections respectively. The median time after injection to onset of benefit was 7 days (range 1-28 days) and to peak benefit was 14 days (range 5-35 days). Median duration of benefit was 9 weeks (range, 3-22 weeks). Although no patient experienced sustained remission following treatment several derived prolonged benefit lasting 6-9 months.

The breakdown of global subjective benefit in relation to the common muscle combinations injected is detailed in Table 2. Clearly, considerable (moderate or excellent) benefit occurred less often after single muscle injections (sternomastoid or splenius capitis) - 58% and 52% respectively - than when a combination of two or more muscles was injected, with considerable benefit after 61-88% of such treatments. There was no significant effect of dose on degree of benefit when this was examined in relation to the most common muscle combination injection, namely sternomastoid and opposite splenius capitis.

Table 3. Torticollis type and response to 429 botulinum toxin treatments in 107 patients

Torticollis type	Number of patients	Response* Nil n†	(%)‡	Mild n	(%)	Moderate n	(%)	Excellent n	(%)	Total
Rotary (simple) torticollis	57	15	(7.1)	38	(18)	99	(46.9)	59	(28)	211
Retrocollis	11	2	(4.3)	4	(8.5)	21	(44.7)	20	(42.6)	47
Laterocollis	15	6	(9.0)	11	(16.4)	37	(55.2)	13	(19.4)	67
Tremulous	9	2	(6.9)	4	(13.8)	16	(55.2)	7	(24.1)	29
Complex	15	7	(9.3)	16	(21.3)	38	(50.7)	14	(18.7)	75

*Global subjective response; †*n* refers to number of treatments; ‡(%) refers to percentage of treatments

Benefit and torticollis type
When global subjective improvement was further analysed according to type of torticollis (Table 3), all variants responded equally well to botulinum toxin injections. There was no clear relation between degree of benefit and duration of torticollis prior to injection.

Adverse effects
Ninety patients (84%) experienced an adverse effect at some time during their treatment. Seventy-nine (74%) developed dysphagia, 34 (32%) dry mouth, 22 (21%) dysphonia and 11 (10%) troublesome neck weakness after one or more treatments. In total, 47% of 483 treatments were associated with adverse effects (Table 4). None of these adverse effects were ever permanent.

Dysphagia Dysphagia was by far the most common and problematic adverse effect, occurring after 211 (44%) of 483 treatments. Median onset was 7 days (range 1-32 days) after treatment, with a median duration of 14 days (range 1-56 days). The degree of dysphagia was not stated after 7% of treatments. It was mild after 30% of treatments, such that no change in dietary habits was required; on occasions a sip of water was required to assist in swallowing hard or dry foodstuffs, for example, bread. After 5% of treatments dysphagia was moderate, whereby some change in dietary habit was required, usually entailing the avoidance of hard or dry foodstuffs (steak, toast etc), and inevitably requiring sips of fluid to aid the ingestion of some solids. On occasions mild choking episodes occurred. Only 2% of treatments were associated with severe dysphagia in nine female and two male patients. On each occasion, the sternomastoid was injected along with the opposite splenius capitis, and on one occasion a trapezius in addition. All patients could only manage sips of fluid at their worst; two required hospitalization for assisted hydration. Two developed stridor and two experienced substantial weight loss. One patient developed a chest infection secondary to aspiration.

Table 4. Adverse effects after 483 botulinum toxin treatments in 107 patients

Adverse effect	Patients n	(%)	Treatments n	(%)
Dysphagia	79	(73.8)	211	(43.7)
Dry mouth/throat	34	(31.8)	44	(9.1)
Dysphonia	22	(20.6)	30	(6.2)
Neck weakness	11	(10.3)	14	(2.9)
Jaw stiffness or weakness	7	(6.5)	12	(2.5)
Limb weakness	6	(5.6)	9	(1.9)
Respiratory symptoms (including stridor)	6	(5.6)	8	(1.7)
Back pain/stiffness	5	(4.7)	7	(1.5)
Tiredness/fatigue	5	(4.7)	6	(1.5)

Dysphagia and muscle combination injected The incidence of dysphagia was analysed according to sites of injection. Overall, the incidence was higher when a sternomastoid was injected (54%) than when treatment did not include a sternomastoid injection (25%; $P<0.01$ Chi-square test). When a sternomastoid was injected in isolation, the overall incidence of dysphagia was 50% but this was always only mild. When other muscles were injected along with the sternomastoid, the overall incidence of dysphagia was similar at 52-55% depending upon the other muscles injected. However, the incidence of moderate or severe dysphagia when sternomastoid was injected along with other muscles was conspicuously higher (12%) than after isolated sternomastoid injection (0%) or combinations not involving sternomastoid (0.5%).

Dysphagia and dose With significant dysphagia only ensuing from injections involving a sternomastoid muscle, we considered the effect of BOTOX dose on the incidence of dysphagia following the 212 sternomastoid and splenius capitis injections. When total dose was 800 MU or more the overall incidence of dysphagia was 64%, and it was moderate or severe in 16%. Doses less than 800 MU resulted in a significantly lower overall incidence of dysphagia (41%, $P<0.01$) and of moderate or severe dysphagia (7%, $P<0.05$ Chi-square test). Similarly, when sternomastoid dose only was considered, the overall incidence of dysphagia when the dose was 400 MU or greater was 61% with moderate or severe dysphagia in 14%, compared with 41% ($P<0.01$) and 7% (not significant) when sternomastoid dose was less than 400 MU.

Other adverse effects (Table 4) Dysphonia, which followed 6% of treatments, only occurred in association with dysphagia and never as an isolated symptom. Jaw/mouth opening stiffness or weakness followed 12 treatments in seven patients, with nine of these treatments being bilateral splenius capitis, and the other three, sternomastoid and splenius capitis combination. One patient with longstanding bilateral leg weakness and muscle wasting from childhood polio reported increasing

weakness of the legs after three treatments, although examination did not confirm clear deterioration in motor function.

Long-term benefit

Of the 107 patients, 101 continued to obtain benefit from repeated injections. Sixty-three of these patients have been treated successfully for more than one year, and some up to 3.5 years. Five patients exhibited diminishing or loss of benefit with successive BOTOX treatments after initially responding well. The serum of these patients along with the serum of five patients showing continued good response was examined for the presence of anti-BOTOX antibodies. In three of those who lost benefit, neutralizing antibodies were detected whilst they were evident (in low titre) in only one of those with continuing benefit. This patient experiences mild 'flu-like symptoms after each of his injections. Subsequently, one of those who appeared to be losing benefit without evidence of neutralizing antibodies, has again had a good response to treatment.

Discussion

This retrospective analysis of 107 patients with torticollis receiving 510 treatments of botulinum toxin represents the largest reported European experience. Improvement was reported after 93% of treatments, with considerable (moderate or excellent) improvement after 76% of treatments. These results are in accord with smaller, uncontrolled studies[7-10], and similar to the only other large uncontrolled trial[11], in which 94% of 505 treatments resulted in benefit, and 60% in substantial benefit. Where pain was present, there was considerable improvement (moderate or excellent) after 66% of treatments, and in many patients, pain disappeared permanently after the first treatment. This prominent relief of pain, common to all studies, raises the possibility of a direct or indirect analgesic property of botulinum toxin even though sensory changes are not a feature of systemic botulism[14].

This is the first study to examine in detail the response of different torticollis variants to botulinum toxin therapy. It was reassuring that dystonic head tremor, complex torticollis, retrocollis and laterocollis all responded as well as the more common rotatory torticollis, with 69-87% of treatments affording considerable (moderate or excellent) benefit.

Previous studies, including our own earlier report[8], employed multiple injections into each muscle. However with experience we have found this to be unnecessary; now we use only one injection per muscle. Despite the larger injection volumes required with this strategy, pain associated with injections has not been a problem; only two patients reported significant pain around the injection site for 1-2 days after treatment. Furthermore, whilst initially we employed EMG guidance to site the injections, now we do not find these necessary or valuable.

The incidence of adverse effects was relatively high, with the majority of patients (84%) experiencing at least one during the course of their treatment. Dysphagia, the most common adverse effect, was experienced by 74% of patients after 44% of treatments. This is the highest incidence thus far reported, excepting our earlier study,. and likely reflects the relatively high doses employed. Indeed, the incidence of dysphagia has been considerably higher in UK (27[9]-32%[5]), than North American studies (0-11%[4,6,7,11,13]). In the UK total doses of 500 mouse units or more have been used, whereas in North America, the total doses have been 275 mouse units or less. Moreover, the UK toxin probably has a higher relative potency than its North American counterpart. Severe dysphagia followed only 2% of treatments and no patients withdrew from treatment because of this adverse effect. Since dysphagia appeared to be related to dose and sternomastoid injection, the sternomastoid dose was reduced from 500 to 300 mouse units (or less in slender women) with subsequent reduction in the incidence of dysphagia during the course of the study period. However, in our experience, reducing the sternomastoid dose further reduces the beneficial effect. In the vast majority who experienced dysphagia, with the doses we have decided upon, the problem was a short-lived minor inconvenience. Because it was always temporary, dysphagia (or other putative adverse effect) which persists for longer than 3 months demands further investigation.

The mechanism of dysphagia and other side effects remains uncertain, but could be via local toxin diffusion or retrograde transport and diffusion to the central nervous system[15,16]. The increased leg weakness reported by the patient with previous polio suggests that patients with pre-existing neuromuscular disorders may be particularly vulnerable to the recognized distant neuromuscular effects of botulinum toxin following neck muscle injections[17].

Three patients who developed resistance to the treatment were shown to have neutralizing antibodies to the botulinum toxin in their serum. This confirms previous observations in a few patients[7,18] and suggests that antibody testing should be undertaken in those patients who demonstrate initial but not subsequent improvement following recurrent injections. The presence of antibodies does not necessarily preclude further successful botulinum toxin treatment as one patient attending our clinic with a high titre of neutralizing antibody responded again when the dose was increased from a total of 1000 to 1600 mouse units per treatment.

On the basis of this large open study and our subsequent experience, we are able to formulate recommendations on the initial treatment of the different torticollis variants for those interested in setting up the technique (Table 1). If this regimen is followed, on the basis of the present results, patients can be advised that there is a 90% chance of some improvement, and more than 70% chance of considerable improvement following each treatment, regardless of the nature of the torticollis. They can also be advised that the risk of dysphagia is approximately 40% if a sternomastoid is injected and 25% if a sternomastoid is not injected, with the risk of significant (moderate or severe) dysphagia being 7% and less than 1% respectively. Finally, they can be warned that there is at least a 3% chance, over the first 15 months of treatment, of antibody production resulting in declining response to treatment.

On the basis of these results and the results of others, botulinum toxin injection must now be considered the mainstay of therapy for spasmodic torticollis. Drug therapy and surgery now are reserved for the minority in whom botulinum toxin injections are impractical or have failed.

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Note

Botulinum toxin A is now marketed in the UK by Porton Products Ltd under the name of 'Dysport'. It is licensed for use in blepharospasm and hemifacial spasm. One vial of 'Dysport' contains 500 mouse units (12.5 ng) of toxin and costs £200.00 (inclusive of VAT). The total cost of one average treatment (800 mouse units) therefore is approximately £320.00, and one year's treatment, £1280.00.